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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	
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12/24/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	09/668,508	YOUNG ET AL.	
	Examiner	Art Unit	
	Thaian N. Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 December 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-51* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-51* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date. _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 12/7/09 has been entered.

Applicants' Amendment and Response, filed 12/7/09, have been entered. Claims 14-17 and 33-35 are cancelled; claims 37-51 are newly added, pending and under current examination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 14-17 and 33-35 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter, is rendered moot in view of Applicants' cancellation of the claims. The newly added claims do not recite that the cells do not form tumors in an animal, which was the basis of this rejection.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 37-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make

and/or use the invention. This is rejection is maintained for reasons of record advanced in the prior Office action.

Enablement is considered in view of the Wands factors (MPEP 2164.01(A)). These include: nature of the invention, breadth of the claims, guidance of the specification, the existence of working examples, state of the art, predictability of the art and the amount of experimentation necessary. All of the Wands factors have been considered with regard to the instant claims, with the most relevant factors discussed below.

Applicants' Arguments. Applicants argue that the prior pending claims have been cancelled, and this rejection is now moot and should be withdrawn. Applicants argue that the newly directed claims are enabled. See pages 9-10 of the specification.

Response to Arguments. These arguments have been considered, but are not persuasive. In particular, the claims encompass the exact same cells that were previously claimed. Although not explicitly recited in the claims that the cells are "embryonic-like", the specification defines the pluripotent animal stem cells as pluripotent, embryonic-like stem cells. Therefore, the enablement issues that were addressed regarding the claimed cells continue to apply to the newly amended claims. The prior rejection of record is maintained and presented below.

The specification teaches that the cell of the claimed invention is a cell that is capable of self-regeneration and differentiation of cells of endodermal, ectodermal and mesodermal lineages. See page 33, 1st ¶. The specification contemplates that these cells are ES-like cells, and thus, broadly interpreted, the claims, as written encompass pluripotent cells, which are art-recognized to have specific qualities. See, for example, Thomson, cited previously. Additionally, the Examiner reiterates that the characterization Applicants' cells are pluripotent is not predictable, as stated previously, and additionally, because the cells express markers that fail to

uniquely identify pluripotent stem cells, such as embryonic stem cells, because these markers as expressed in other cell types. The Examiner presented these arguments in the prior Office actions. In particular, the cells that the specification teaches expresses markers in EC cells, which are not expressed in ES cells, and further, it is noted that EC cells are different than ES cells in various ways, including differentiation potential. Additionally, the specification teaches that the cells express alkaline phosphatase, however, this marker fails to particularly identify a single cell type because this marker is expressed in other cell types (see Pera, Eiges, Gerecht-Nir, cited previously). Similarly, the specification teaches that the claimed cells express SSEA-4 (indicated by MC-813-70). See Table 7. Although SSEA-4 is a marker that is expressed in human ES cells, it is also expressed in mesenchymal stem cells; see Gang (cited previously). Therefore, these markers fail to specifically characterize a particular cell.

The specification teaches that the pluripotent embryonic-like stem cells are isolated from various postnatal tissues and the cells were analyzed for differentiation capacity and expression of various markers. In particular, the specification teaches analysis of CF-NHDF2 (a dermis cell line), was incubated with dexamethasone and insulin for 45 days and examined morphologically, immunochemically and histochemically. See Example 9, p. 160. Additionally, the cell lines CM-SKM1 and CF-SkM2 were analyzed. The specification teaches that the cells were evaluated for alkaline phosphatase expression (indicating pluripotency), as well as extended capabilities for self-renewal, high levels of telomerase activity and induced differentiated cell types showing phenotypic markers for various tissue types. The specification further teaches that that these results indicate that the cells are pluripotent, embryonic-like stem cells. Tables 6-10 teach various markers that were tested, in particular, embryonic markers SSEA-1, SSEA-3, SSEA-4, H-CD34, H-CD66, and alkaline phosphatase were tested.

Furthermore, the claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. Thus, although specification has shown that the claimed cells express alkaline phosphatase and SSEA-4, this does not provide sufficient guidance to show that these cells are pluripotent. The claims do not meet the definitions for a pluripotent cell, as set forth by the cited art above.

With regard to claim 46, wherein the cells express SSEA4 and CD10, Applicants are referred to the prior Office actions, which shows that pluripotent cells, such as ES cells, have specific characteristics, including differentiation potential, morphology, as well as specific cell markers, which define these cells. The claims are broadly directed to cells from any species, thus, there is no teaching, with regard to expression markers from cells other than human. CD10 is also expressed in various cell types. Applicants' cells would not be considered pluripotent, because they express markers and have phenotypes and characteristics that fail to establish that they are pluripotent. It is unclear what type of cell(s) are encompassed by Applicants' cells because they do not possess many of the art-recognized characteristics of pluripotent cells. The characterization of a cell as pluripotent not only refers to its differentiation potential, but specific markers that serve to define these cells.

Accordingly, in view of the lack of teachings or guidance provided by the specification, with regard to the identification and characterization of the claimed cells, the state of the art, which clearly shows that using particular markers fails to establish or uniquely identify ES cells, it would have required undue experimentation for one of ordinary skill in the art to make and use the claimed cells.

Written Description

Claims 37-51 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection is maintained for reasons of record, advanced in the prior Office action.

Applicants' Arguments. Applicants argue that the skilled artisan given his/her significant knowledge and skill and the teachings of the specification, could readily recognize that Applicants have possession of the invention. Applicants argue that the prior claims have been cancelled, and thus, the rejection is moot and should be withdrawn. See p. 10 of the Response.

Response to Arguments. These arguments have been considered, but are not persuasive. In particular, the claims encompass the exact same cells that were previously claimed. Therefore, the written description issues that were addressed regarding the claimed cells continue to apply to the newly amended claims. The prior rejection of record is maintained and presented below.

Vas-Cath Inc. v. Mahurkar 19USPQ2d 1111 (Fed. Cir. 1991), clearly states that, "[A]pplicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of *the invention*. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed*." *Vas-Cath Inc. v. Mahurkar,* 19USPQ2d at 1117. The specification does not, "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." *Vas-cath Inc. v. Mahurkar*, 19USPQ2d at 1116.

The specification teaches the analysis of various human cell lines that were isolated from postnatal tissues, and has determined that these cells are pluripotent, embryonic-like stem cells, based upon their ability to differentiate into various cell types, as well as markers expressed by the cells themselves. However, the

specification fails to provide sufficient, identifying characteristics of the claimed cells such that one of skill in the art would recognize that Applicants had possession of the claimed cells.

The Examiner notes that Table 7 teaches differential expression markers of EC cells, and alkaline phosphatase, as well as SSEA-4 in conditions that include insulin and dexamethasone for the CF-NHDF2 cell line. Table 8 shows that the cells, after 37 doublings, do not express alkaline phosphatase, but at 40 doublings, express alkaline phosphatase, and after 45 doublings, no expression of alkaline phosphatase is noted. Cell line CM-SKM2 did not show any expression of alkaline phosphatase or SSEA-4 (Table 10). As shown in prior Office actions and above, these markers are expressed in pluripotent cells, but not uniquely. Additionally, the markers that are claimed are not consistently expressed by Applicants' cells, and therefore do not provide a positive identifying characteristic for the cells.

Thus, it is unclear from Applicants' results what markers are expressed (or not) in the claimed cells, such that one of skill in the art could readily identify that Applicants had possession of the claimed cells. Specifically, the specification fails to describe the markers and specific characterization of the cells (such as teratoma formation), and the skilled artisan, although recognizing that specific markers and characteristics identify pluripotent cells, could not envision which of such markers or characteristics, would uniquely identify Applicants' claimed cells.

See *Fiers v. Revel,* 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016 (Fed. Cir. 1991).

One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481, 1483. In *Fiddes*, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification only provided the bovine sequence.

Applicant is reminded that *Vas-Cath* makes clear that the written description of 35 U.S.C. 112 is severable from its enablement provision [see p. 1115].

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 41-43 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 41-43 recite the limitation "The stem cells of claim 37" in line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 37 relates to a single, not plurality of stem cells.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 37, 38, 40-43, 45, 48, 49, 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Capecchi *et al.* [**Scientific American**, 270(3):34-41 (1994), of record].

It is noted that the limitation in the claims that the cells are isolated from a postnatal source fails to distinguish the claimed cells from the cells of the art. The

cells taught by Capecchi have the exact same characteristics as the required by the instantly claimed cells (*i.e.,* capable of self-renewal and differentiation to cells of endodermal, ectodermal and mesodermal lineages). The claims are not distinguished from the art.

Capecchi teach the inactivation of target genes by homologous recombination, and the insertion of a *neo* resistance gene, which serves as a positive selection marker in mouse ES cells. See Figure, p. 36. They teach that the ES cells are then cultured and grown into surrogate mothers to generate chimeric mice. See p. 38, Figure. Note that the claimed cells are not distinguished from those taught by Capecchi. Capecchi fulfills the limitations of the claims (the differentiation to cells of any endodermal, ectodermal, mesodermal lineage) by showing the generation of mice; further, the methods of producing the genetically engineered cells are also anticipated by Capecchi because they teach transfection of pluripotent embryonic-like stem cells. Accordingly, Capecchi anticipate the claims.

Claims 37, 40-43, 45, 48, 49, 51 are rejected under 35 U.S.C. 102(b) as being anticipated by Piedrahita *et al.*

Piedrahita teach the generation of transgenic porcine chimeras using primordial germ cells (PGCs)-derived colonies. In particular, they teach the isolation of the PGCs from 25-27 day old pig fetuses, (p. 1321, 2nd column, Methods & Materials), they show the ability of the PGC to survive and proliferate in an undifferentiated state (see p. 1322, 1st column, AP Staining), the ability of the PGCs to differentiate into embryoid bodies (p. 1322, 1st column), the transformation of PGCs by electroporation using a plasmid that contained humanized GFP (p. 1322, col. 1-2) and the generation of chimeric pig fetuses and pigs using the transformed PGCs.

Piedrahita *et al.* anticipate the claimed invention because the PGCs they teach are capable of differentiation into the three germ layers (as evidenced by both

the generation of embryoid bodies and the generation of chimeric pig fetuses and chimeric piglets). Chimeric animals, by definition, have some cells have cells that are contributed by the donor cells, and some from the cells of the recipient blastocysts. Piedrahita teach the analysis of transgene expression and show that the pigs expressed the transgene in different tissues, they teach that analysis of the developing fetuses suggests that although some may have germ line transmission, it would require that the chimeric cells contribute to the germ line. See p. 1328, 2nd column, 2nd full ¶, and p. 1329, 1st column, 2nd ¶. Accordingly, Piedrahita anticipate the claimed invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 37-45, 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Shamblott when taken with Sambrook *et al.* This rejection is maintained for reasons of record.

Applicants' Arguments. Applicants argue that the instantly claimed cells are distinguished from the cells taught by Shamblott and traverse this rejection. Applicants argue that additionally, the prior claims 14-17 are cancelled, rendering this rejection moot. See pages 11-12 of the Response.

Response to Arguments. These arguments are fully considered, but are not persuasive. The claims do not distinguish between the cells of Shamblott and the cells that are instantly claimed. As stated above and previously, the instantly claimed cells are not found to be distinguished by that of the art because there are no requisite characteristics that differentiate them from, for example, the PGCs taught by Shamblott. Shamblott teaches that the PGCs are pluripotent, as are the claimed cells. The specification teaches that a pluripotent stem cell is capable of self-regeneration, differentiation to cells of endodermal, ectodermal and mesodermal lineages (see p. 35-36). These properties are found in the cells taught by Shamblott. Thus, the prior rejection is maintained.

Shamblott *et al.* teach the generation of human pluripotent stem cells from gonadal ridges and mesenteries containing primordial germ cells [PGCs] and teach that embryoid bodies collected from these cultures revealed a wide variety of differentiated cell types, including derivatives of all three embryonic germ layers [see *Abstract*]. In particular, Shamblott *et al.* teach that gonadal ridges and mesenteries of 5 to 9 week old human fetuses and cells initially cultured on a layer of mouse STO fibroblast feeder layer. The cells formed embryoid bodies, which were collected and analyzed immunohistochemically [see pp. 13726-13727, *Materials & Methods*]. It was found that the embryoid bodies demonstrated derivatives of the three embryonic germ layers [see p. 13729, 2nd column and Table 1]. Note that Shamblott teach the pluripotent embryonic-like stem cells because the claims do not

provide any requisite characteristics (*e.g.*, specific markers, etc.) of the claimed embryonic-like stem cells such that they would be distinguished from the cells taught by Shamblott. The claims recite that the embryonic-like stem cells are "derived from non-embryonic or postnatal animal cells or tissue;" however, this recitation does not differentiate them from the cells as taught by Shamblott. Further, the method claim has been included in this rejection because the cells as instantly claimed are not distinguishable from those taught in the art. The cells as taught by Shamblott fulfill the requirements of the claims because they are capable of differentiation to cells of each and any of endodermal, ectodermal and mesodermal lineages, and are capable of self-renewal.

Shamblott do not teach the transfection of the pluripotent stem cells to produce a genetically engineered pluripotent stem cell. However, prior to the time of the claimed invention, Sambrook teach methods of transfecting mammalian cells with any gene of interest [see 16.33-16.38]. Accordingly, in view of the combined teachings of Shamblott and Sambrook, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to use the PGCs, as taught by Shamblott and transfect them with any DNA of interest, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as expression of proteins in mammalian cells can provide different purposes, as described by Sambrook on p. 16.3, such as for the expression of large amounts of protein of biological interest, or to study the biosynthesis and intracellular transport of proteins following their expression in various cell types.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Claims 37-45, 47-51 are rejected under 35 U.S.C. 103(a) as being unpatentable over Thomson (**Science**, 282: 1145-1147, 1998, IDS). when taken with Sambrook *et al.* (cited previously).

Thomson teach the isolation of human ES cells. See p. 1145, col. 2. The cells are capable of maintaining an undifferentiated state and proliferate indefinitely, and have the potential to differentiate into derivatives of all three embryonic germ layers. They teach that the cells differentiated into cells of endoderm, mesoderm and ectoderm. Note that the claims fail to distinguish the claimed cells from the cells taught by Thomson. Thus, the method claim has been included in the rejection because the cells used in the method are not distinguished from those taught by Thomson. Thomson do not teach that the ES cells are genetically engineered to express a gene or protein of interest.

However, prior to the time of the claimed invention, Sambrook teach methods of transfecting mammalian cells with any gene of interest [see 16.33-16.38]. Accordingly, in view of the combined teachings of Thomson and Sambrook, it would have been obvious for one of ordinary skill in the art at the time the claimed invention was made, to use the pluripotent embryonic stem cells, as taught by Thomson and transfect them with any DNA of interest, with a reasonable expectation of success. One of skill in the art would have been sufficiently motivated to make such a modification, as expression of proteins in mammalian cells can provide different purposes, as described by Sambrook on p. 16.3, such as for the expression of large amounts of protein of biological interest, or to study the biosynthesis and intracellular transport of proteins following their expression in various cell types.

Thus, the claimed invention, as a whole, is clearly *prima facie* obvious in the absence of evidence to the contrary.

Conclusion

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632